**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings of claims in the application:

**Listing of Claims:**

1. (Currently amended) [[A]] An isolated polypeptide comprising an antibody heavy chain variable region and an antibody light chain variable region, the polypeptide having at least 5 times higher binding affinity for an antigen ~~bound by a parental antibody~~ relative to the affinity of ~~the~~ a parental antibody for the same antigen, the polypeptide having a sequence that (a) differs from the parental antibody by an amino acid substitution of at least one amino acid in a complementarity determining region (CDR), the amino acid in the parental antibody being encoded by a codon that comprises a nucleotide belonging to a hot spot motif selected from AGY or RGYW, wherein R is A or G, Y is C or T and W is A or T, and (b) does not differ from the parental antibody in the amino acids in the CDR with respect to amino acids encoded by a codon that does not belong to one of these two hot spot motifs.

2. (Previously presented) The polypeptide of claim 1 wherein the substitution occurs in CDR3 of the light chain variable region.

3. (Previously presented) The polypeptide of claim 1 wherein the substitution occurs in CDR3 of the heavy chain variable region.

4. (Previously presented) The polypeptide of claim 1 wherein the substitution occurs in CDR1 or CDR2 of the light chain variable region.

5. (Previously presented) The polypeptide of claim 1 wherein the substitution occurs in CDR1 or CDR2 of the heavy chain variable region.

6-7. (Canceled)

8. (Original) The polypeptide of claim 1, wherein said polypeptide is a scFv.

9. (Canceled)

10. (Original) The polypeptide of claim 1, wherein said polypeptide is a dsFv, a Fab, or a F(ab' )2.

11. (Canceled)

12. (Currently amended) The polypeptide of claim 1 ~~further comprising~~ , fused or conjugated to a therapeutic moiety or a detectable label.

13. (Original) The polypeptide of claim 12, wherein the therapeutic moiety is a toxic moiety.

14. (Currently amended) The polypeptide of claim 13, wherein the toxic moiety is a *Pseudomonas* exotoxin A ("PE") ~~or a cytotoxic fragment thereof~~.

15. (Currently amended) The polypeptide of claim 14, wherein the toxic moiety is ~~a cytotoxic fragment, which is~~ selected from the group consisting of PE35, PE40, and PE38.

16. (Original) The polypeptide of claim 13, wherein the toxic moiety is selected from the group consisting of diphtheria toxin or a cytotoxic fragment thereof, saporin or a cytotoxic fragment thereof, pokeweed antiviral toxin or a cytotoxic fragment thereof, ricin or a cytotoxic fragment thereof, and bryodin 1 or a cytotoxic fragment thereof.

17-20. (Canceled)

21. (Previously presented) The polypeptide of claim 1, expressed in conjunction with surface protein gIIIp of a filamentous bacteriophage.

22-26. (Canceled)

27. (Currently amended) [[A]] An isolated nucleic acid molecule encoding a polypeptide comprising an antibody heavy chain variable region and an antibody light chain variable region, the polypeptide having at least 5 times higher binding affinity for an antigen ~~bound by a parental antibody~~ relative to the affinity of ~~the~~ a parental antibody for the same antigen, the polypeptide having a sequence that (a) differs from [[a]] the parental antibody by an amino acid substitution of at least one amino acid in a complementarity determining region (CDR), the amino acid in the parental antibody being encoded by a codon that comprises a nucleotide belonging to a hot spot motif selected from AGY or RGYW, wherein R is A or G, Y is C or T and W is A or T, and (b) does not differ from the parental antibody in the amino acids within the CDR with respect to amino acids not encoded by a codon with a nucleotide belonging to a hot spot motif selected from AGY or RGYW.

28-30. (Canceled)

31. (Original) An expression cassette comprising a promoter operably linked to a nucleic acid molecule of claim 27.

32. (Canceled)

33. (Currently amended) A method of killing a malignant cell bearing an antigen, comprising contacting the cell with an ~~immunotoxin~~ immunoconjugate comprising a toxic moiety and a targeting moiety, the targeting moiety comprising a polypeptide comprising an antibody heavy chain variable region and an antibody light chain variable region, the polypeptide having at least 5 times higher binding affinity for ~~an~~ the antigen ~~bound by a parental antibody~~

relative to the affinity of ~~the~~ a parental antibody for the ~~same~~ antigen, the polypeptide having a sequence that (a) differs from the parental antibody by an amino acid substitution of at least one amino acid in a complementarity determining region (CDR), the amino acid in the parental antibody being encoded by a codon that comprises a nucleotide belonging to a hot spot motif selected from AGY or RGYW, wherein R is A or G, Y is C or T and W is A or T, and (b) does not differ from the parental antibody in the sequence of amino acids within the CDR with respect to amino acids not encoded by a codon with a nucleotide belonging to a hot spot motif selected from AGY or RGYW.

34. (Original) The method of claim 33, wherein the antigen is mesothelin.

35. (Currently amended) The method of claim 34, wherein the targeting moiety has a sequence that varies from SS antibody (SEQ ID NO:1) by having substitutions selected from the group consisting of G93K-Y94H (SS1); S92G-G93F-Y94N (D8) and S92G-G93S-Y94H (C10), which amino acids are numbered as in Figure 3.

36. (Currently amended) The method of claim 35, wherein said toxic moiety is a *Pseudomonas* exotoxin A ("PE") ~~or cytotoxic fragment thereof~~.

37. (Currently amended) The method of claim 36, wherein the toxic moiety is ~~a cytotoxic fragment,~~ selected from the group consisting of PE35, PE38, and PE40.

38-40. (Canceled)

41. (Withdrawn) A method of identifying a polypeptide which has a higher affinity for a target antigen than does a parental antibody, comprising

(a) contacting a polypeptide of claim 1 with the target antigen under conditions appropriate for specific binding between an antibody and the target antigen,

(b) eluting the polypeptide under conditions which remove any antibody or fragment thereof which have not bound to the target antigen with an affinity higher than that of the parental antibody or fragment thereof, and

(c) determining whether the polypeptide is bound to the antigen, whereby binding identifies the polypeptide as having a higher affinity for the target than does the parental antibody.

42. (Withdrawn) A method of making a library of nucleic acids encoding mutated antibody variable domains comprising:

a) providing a nucleic acid molecule encoding an amino acid sequence of a VH or a VL domain of a parental antibody, the nucleic acid molecule comprising at least one parental hot spot codon comprising at least one nucleotide within a hot spot motif;

b) generating a plurality of mutated nucleic acid molecules encoding mutated amino acid sequences that differ from the parental amino acid sequence wherein each mutated nucleic acid sequence comprises at least one mutated codon different than a parental hot spot codon encoding an amino acid, the mutated codon encoding an amino acid different than the amino acid encoded by the parental hot spot codon.

43. (Withdrawn) The method of claim 42 wherein the plurality of mutated nucleic acid molecules contains at least 19 members, wherein each of the 19 members encodes an amino acid sequence in which the amino acid encoded by the parental hot spot codon is replaced by a different natural amino acid.

44. (Withdrawn) The method of claim 42, wherein the plurality of mutated nucleic acid molecules comprises mutated codons different than at least two parental hot spot codons encoding amino acids, each of the mutated codons encoding an amino acid different than the amino acid encoded by the parental hot spot codon.

45. (Withdrawn) The method of claim 42, wherein the plurality of mutated nucleic acid molecules comprises at least 399 members, each of which members encodes an amino acid sequence in which the amino acids encoded by the parental hot spot codons is replaced by a different natural amino acid.

46. (Withdrawn) The method of claim 42, further wherein the parental antibody is of a class of antibodies having at least one conserved amino acid encoded by a codon, wherein the codon or codons encoding the conserved amino acids are not mutated.

47. (Withdrawn) The method of claim 42, wherein the hot spot motif is selected from the group consisting of AGCA, AGTT, AGCT, AGTA, GGCA, GGTT, GGCT, GGTA, AGC, and AGT.

48. (Withdrawn) The method of claim 42, wherein the mutated nucleic acid molecule comprises at least one mutated codon within a portion of the VH or the VL domain comprising a CDR.

49. (Withdrawn) The method of claim 48, wherein the CDR is the CDR3 of the VH domain.

50. (Withdrawn) The method of claim 48, wherein the CDR is the CDR3 of the VL domain.

51-68. (Canceled)

69. (New) An isolated anti-mesothelin antibody comprising a variable heavy ("$V_H$") chain and a variable light ("$V_L$") chain, which $V_H$ and $V_L$ chains each have a first, a second and a third complementarity-determining region ("CDR"), wherein the first CDR ("CDR1"), the second CDR ("CDR2"), and third CDR ("CDR3"), respectively, of said heavy chain have the amino acid residue sequence shown for CDR1, CDR2, and CDR3, respectively, of the heavy chain shown in Figure 1, and wherein CDRs 1, 2 and 3 respectively, of said $V_L$ chain, have the amino acid

residue sequence shown for CDR1, CDR2, and CDR3, respectively, of the light chain shown in Figure 1, provided that the sequence of amino acid residues in CDR3 of the $V_L$ chain differs from that shown in Figure 1 by a substitution of at least one amino acid selected from S92, G93, Y94, and L96, which amino acids are numbered as in Figure 3.

70. (New) An isolated anti-mesothelin antibody of claim 69, wherein the substitutions are selected from G93K-Y94H (antibody SS1); S92G-G93F-Y94N (antibody D8), S92G-G93S-Y94H (antibody C10), and L96T (antibody E4), said amino acid residues being numbered as in Figure 3.

71. (New) An isolated anti-mesothelin antibody of claim 69, wherein said antibody is a scFv, dsFv, a Fab, or a $F(ab')_2$

72. (New) An isolated anti-mesothelin antibody of claim 69, further comprising an amino acid substitution of at least one amino acid in a CDR selected from the group consisting of $V_L$ CDR1, $V_L$ CDR2, $V_H$ CDR1, and $V_H$ CDR2, said amino acid being encoded by a codon that comprises a nucleotide belonging to a hot spot motif selected from AGY or RGYW, wherein R is A or G, Y is C or T and W is A or T.

73. (New) A chimeric molecule comprising a isolated anti-mesothelin antibody of claim 69 and a therapeutic moiety or a detectable label.

74. (New) A chimeric molecule of claim 73, wherein the therapeutic moiety is a toxic moiety.

75. (New) A chimeric molecule of claim 74, wherein the toxic moiety is a *Pseudomonas* exotoxin A ("PE").

76. (New) A chimeric molecule of claim 75, wherein the PE is selected from the group consisting of PE35, PE38, and PE40.

77. (New) A chimeric molecule of claim 73, wherein said antibody further comprises an amino acid substitution of at least one amino acid in a CDR selected from the group consisting of $V_L$ CDR1, $V_L$ CDR2, $V_H$ CDR1, and $V_H$ CDR2, said amino acid being encoded by a codon that comprises a nucleotide belonging to a hot spot motif selected from AGY or RGYW, wherein R is A or G, Y is C or T and W is A or T.

78. (New) A composition comprising (a) a chimeric molecule of claim 73 and, (b) a pharmaceutically acceptable carrier.

79. (New) A method of killing a malignant cell bearing mesothelin antigen, said method comprising contacting the cell with a chimeric molecule comprising a toxic moiety and a targeting moiety, wherein the targeting moiety has a variable heavy ("$V_H$") chain and a variable light ("$V_L$") chain, which $V_H$ and $V_L$ chains each have a first complementarity determining region ("CDR"), a second CDR and a third ("CDR"), respectively, wherein the first CDR ("CDR1"), the second CDR ("CDR2"), and third CDR ("CDR3"), respectively, of said heavy chain have the amino acid residue sequence shown for CDR1, CDR2, and CDR3, respectively, of the heavy chain shown in Figure 1, and wherein CDRs 1, 2 and 3 respectively, of said $V_L$ chain, have the amino acid residue sequence shown for CDR1, CDR2, and CDR3, respectively, of the light chain shown in Figure 1, provided that the sequence of amino acid residues in CDR3 of the $V_L$ chain differs from that shown in Figure 1 by a substitution of at least one amino acid selected from S92, G93, Y94, and L96, which amino acids are numbered as in Figure 3.

80. (New) A method of claim 79, wherein the substitutions are selected from G93K-Y94H (antibody SS1); S92G-G93F-Y94N (antibody D8), S92G-G93S-Y94H (antibody C10), and L96T (antibody E4), which amino acids are numbered as in Figure 3.

81. (New) A method of claim 79, wherein said toxic moiety is a *Pseudomonas* exotoxin A ("PE").

82. (New) A method of claim 81, wherein the PE is selected from the group consisting of PE35, PE38, and PE40.

83. (New) A method of claim 79, wherein said targeting moiety further comprises an amino acid substitution of at least one amino acid in a CDR selected from the group consisting of $V_L$ CDR1, $V_L$ CDR2, $V_H$ CDR1, and $V_H$ CDR2, said amino acid being encoded by a codon that comprises a nucleotide belonging to a hot spot motif selected from AGY or RGYW, wherein R is A or G, Y is C or T and W is A or T

84. (New) An isolated nucleic acid molecule encoding an anti-mesothelin antibody comprising a variable heavy ("$V_H$ ") chain and a variable light ("$V_L$ ") chain, which $V_H$ and $V_L$ chains each have a first, a second and a third complementarity-determining region ("CDR"), wherein the first CDR ("CDR1"), second CDR ("CDR2")and third CDR ("CDR3"), respectively, of said heavy chain have the amino acid residue sequence shown for CDR1, CDR2, and CDR3, respectively, of the heavy chain shown in Figure 1, and wherein the first CDR ("CDR1"), second CDR ("CDR2") and third CDR ("CDR3"), respectively, of said $V_L$ chain, have the amino acid residue sequence shown for CDR1, CDR2, and CDR3, respectively, of the light chain shown in Figure 1, provided that the sequence of amino acid residues in the third CDR of the $V_L$ chain differs from that shown in Figure 1 by a substitution of at least one amino acid selected from S92, G93, Y94, and L96, which amino acids are numbered as in Figure 3.

85. (New) A nucleic acid molecule of claim 84, wherein the substitutions are selected from G93K-Y94H (antibody SS1); S92G-G93F-Y94N (antibody D8), S92G-G93S-Y94H (antibody C10), and L96T (antibody E4), which amino acids are numbered as in Figure 3.

86. (New) A nucleic acid of claim 84, wherein said antibody further comprises an amino acid substitution of at least one amino acid in a CDR selected from the group consisting of the $V_L$ CDR1, the $V_L$, CDR2, the $V_H$ CDR1, and the $V_H$ CDR2, said amino acid being encoded by a codon that comprises a nucleotide belonging to a hot spot motif selected from AGY or RGYW, wherein R is A or G, Y is C or T and W is A or T

87. (New) An expression cassette comprising an isolated nucleic acid of claim 84 operably linked to a promoter.

88. (New) An expression cassette of claim 87, further wherein the anti-mesothelin antibody encoded by said nucleic acid has substitutions selected from the group consisting of G93K-Y94H (antibody SS1); S92G-G93F-Y94N (antibody D8), S92G-G93S-Y94H (antibody C10), and L96T (antibody E4), which amino acids are numbered as in Figure 3.

89. (New) An expression cassette of claim 87, further wherein antibody further comprises an amino acid substitution of at least one amino acid in a CDR selected from the group consisting of the first CDR of $V_L$, the second CDR of $V_L$, the first CDR of $V_H$, and the second CDR of $V_H$, said amino acid being encoded by a codon that comprises a nucleotide belonging to a hot spot motif selected from AGY or RGYW, wherein R is A or G, Y is C or T and W is A or T.